

## EDITORIAL COMMENT

### Basic Cardiovascular Research and its Implications for the Medicinal Use of Nicotine\*

Neal L. Benowitz, MD  
*San Francisco, California*

The cardiovascular pharmacology of nicotine is complex. Nicotine acts on nicotinic cholinergic receptors in neural tissues and in muscle, as well as in the skin, bronchial tree, endothelial cells, and vascular smooth muscle. These receptors are physiologically activated by acetylcholine. The pharmacodynamics of nicotine are complex, as dose-response curves are often biphasic, and tolerance develops rapidly to many effects of nicotine, with variable rates and extent of development of tolerance for different responses (1,2). It is in this context of a complex pharmacology that one needs to interpret basic science cardiovascular research on nicotine and the relevance of such studies to human smoking and the medicinal use of nicotine.

See pages 482 and 489

The two studies in this issue of the *Journal* describe novel effects of nicotine in animals or cell preparations. Heeschen and co-workers (3) show that nicotine enhances arteriogenesis in ischemic rabbit hind limbs. Nicotine was shown to stimulate the expression of monocyte and endothelial adhesion molecules and to increase the release of monocyte chemoattractant protein-1 (MCP-1). The result was increased endothelial cell proliferation and increased monocyte adhesion and migration across endothelial cells. This work builds on two other recent studies from the same group of researchers. In one report, nicotine was shown to stimulate angiogenesis by acting on endothelial cell  $\alpha$ -7 nicotinic cholinergic receptors (4). In another report, increased endothelial cell growth in response to nicotine in vitro and in a mouse model of hind limb ischemia was observed (5). Nicotine increased capillary growth and enhanced tissue perfusion. Also in a mouse model, nicotine enhanced the growth of lung cancer implants and stimulated the growth of atherosclerotic plaques. The angiogenesis effect was found to be mediated by the release of nitric oxide, prostacyclin, and vascular endothelial growth factor (5).

The study by Suzuki et al. (6) in this issue of the *Journal* shows that nicotine inhibits apoptosis of cardiac myocytes

induced by lipopolysaccharide in rats. This study raises the possibility that nicotine could be protective against myocardial cell necrosis and fibrosis, such as occurs in heart failure. Both studies raise questions about the possible toxicity and therapeutic benefit of nicotine.

Concerns about cardiovascular toxicity of nicotine arise in two areas. The first is the contribution of nicotine to the pathogenesis of cardiovascular disease that occurs in cigarette smokers. The second concern is toxicity in people who may be using nicotine as a medication to aid tobacco cessation, or in the potential use of nicotine (or nicotinic cholinergic agonist compounds) for medical diseases such as ulcerative colitis, Alzheimer's disease, and depression, among others.

Because of the complex dose-response and tolerance issues, it is not easy to extrapolate basic science studies of nicotine in animals or cell preparations to the effects of nicotine in people. For example, Heeschen et al. (5) have indicated that the mechanism by which nicotine promotes angiogenesis is via stimulation of endothelial cell production or release of nitric oxide and/or prostacyclin. The release of nitric oxide and prostacyclin is known to result in the dilation of blood vessels and in the reduction of platelet aggregation, effects generally thought to be protective against vascular ischemia. Viewed in this context, nicotine would be thought of as beneficial rather than detrimental to cardiovascular function. However, some studies in humans suggest that nicotine does not increase but rather decreases nitric oxide release (7), quite the opposite of the findings in mice. A study of nicotine patch use in humans found no effect on prostacyclin release (8). Thus, it is not at all clear that the mechanisms by which nicotine promotes angiogenesis in mice are operative in humans receiving nicotine.

Mechanistic studies such as those published by Heeschen and co-workers and by Suzuki are important in elucidating cardiovascular cholinergic pharmacology and the possible role of the cholinergic nervous system in the pathogenesis of cardiovascular disease. However, such studies often focus on particular pathophysiological processes in susceptible animal models, rather than the effects of nicotine on a functionally intact organism over time. Therefore, the effects of nicotine in people, in doses and dosing routes produced by nicotine medications, cannot be predicted by research studies in mice or rabbits. We need long-term clinical observations of nicotine exposure in people to determine whether nicotine produces harmful effects in humans.

With respect to the role of nicotine in causing cardiovascular disease, there is a body of evidence in smokeless tobacco users that is reassuring. Smokeless tobacco delivers as much nicotine as does regular cigarette smoking, but it does not expose the user to oxidant gases, carbon monoxide, and other products in tobacco smoke that are toxic to the cardiovascular system (9,10). Studies of cardiovascular risk factors, including inflammatory markers and markers of platelet activation, suggest that cigarette smoking is injurious but the use of smokeless tobacco is not (10). Case-

\*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

From the Division of Clinical Pharmacology and Experimental Therapeutics, Medical Service, San Francisco General Hospital Medical Center, the Departments of Medicine, Psychiatry, and Biopharmaceutical Sciences, University of California, San Francisco, California. The author was supported by grants DA02277 and DA12393 from the United States Public Health Service, National Institute on Drug Abuse, National Institutes of Health, Bethesda, Maryland. He is an occasional paid consultant to pharmaceutical companies that manufacture and market medications to aid smoking cessation, including nicotine products.

control studies in Sweden, where snuff use is widespread, show the expected association between cigarette smoking and myocardial infarction, but no excess risk of myocardial infarction in snuff users compared to people who use no tobacco (11,12). These observations suggest that nicotine per se is not a substantial cause of cardiovascular disease.

Comparing cigarette smoking and nicotine medications, it is evident that nicotine is quite safe compared to smoking. Clinical trials of nicotine therapy to aid smoking cessation in smokers with cardiovascular disease have shown no evidence of increased risk (13). In fact, smokers who continue to smoke but smoke fewer cigarettes while using nicotine patches, despite higher levels of nicotine in the blood, demonstrate less ischemia during exercise compared to before taking nicotine medication (14).

Of course, the possibility exists that long-term use of nicotine as a medication could have adverse cardiovascular effects in a nonsmoker. In addition to the effects to enhance angiogenesis described by Heesch et al. (3,4), nicotine may induce endothelial cell dysfunction and possibly induce insulin resistance, both of which are significant risk factors for cardiovascular disease (7,15,16). Nicotine also appears to promote lipolysis, which could contribute to adverse lipid profiles (17).

Although cardiovascular toxicity has been the major concern of most nicotine research in the past, the present studies suggest the possibility that nicotine could have beneficial effects. Angiogenesis and inhibition of apoptosis could be useful in preserving myocardial function in patients with ischemic heart disease and other types of myocardial injury. However, studies of smokers show that cigarette smoking is a major risk factor for the progression of ischemic heart disease and of congestive heart failure (18). Thus, evidence of a beneficial effect of nicotine in smokers is presently lacking. Of course, numerous other potential cardiovascular toxins in cigarette smoke could explain deterioration in smokers despite potential beneficial effects of nicotine per se, so the therapeutic potential for nicotine in cardiovascular disease remains an open question.

In summary, nicotine has a very complex pharmacology. This is because nicotinic cholinergic receptors perform many functions, with different levels of activity and distribution in different parts of the body, and different responses depending on dose and duration of acetylcholine exposure. Nicotine activates multiple neurohormonal systems that can have additive or opposing effects. For drug development, one would like the most specific drug effects possible, and perhaps nicotinic cholinergic receptor subtype-specific agonists could be developed that have beneficial cardiovascular effects without having adverse effects on other systems. With respect to nicotine toxicity, only human studies in which the various interacting effects of nicotinic receptor stimulation are in play can determine whether nicotine produces cardiovascular harm or benefit in people.

Finally, considering the risks and benefits of nicotine, even if the concerns about toxicity related to arteriogenesis raised by Heesch et al. are valid, this would not diminish

the overwhelming benefit of nicotine medications to aid cessation in smokers. Cigarette smoke delivers not only nicotine at high doses but also a myriad of other toxins that damage blood vessels and cause cancer. The use of nicotine to stop smoking or to reduce smoking in someone who would otherwise not quit is unquestionably safer than continued smoking. Basic scientific findings regarding the cardiovascular toxicity of nicotine should not dissuade health providers or patients from using nicotine to treat tobacco dependence, even in smokers with known cardiovascular disease.

**Reprint requests and correspondence:** Dr. Neal L. Benowitz, Chief, Division of Clinical Pharmacology and Experimental Therapeutics, University of California, San Francisco, Box 1220, San Francisco, California 94143-1220. E-mail: nbeno@itsa.ucsf.edu.

## REFERENCES

1. Benowitz NL. Pharmacologic aspects of cigarette smoking and nicotine addiction. *N Engl J Med* 1988;319:1318-30.
2. Fattinger K, Verotta D, Benowitz NL. Pharmacodynamics of acute tolerance to multiple nicotinic effects in humans. *J Pharmacol Exp Ther* 1997;281:1238-46.
3. Heesch C, Weis M, Cooke JP. Nicotine promotes collateral growth. *J Am Coll Cardiol* 2003;41:489-96.
4. Heesch C, Weis M, Aicher A, Dimmeler S, Cooke JP. A novel angiogenic pathway mediated by non-neuronal nicotinic acetylcholine receptors. *J Clin Invest* 2002;110:527-36.
5. Heesch C, Jang JJ, Weis M, et al. Nicotine stimulates angiogenesis and promotes tumor growth and atherosclerosis. *Nat Med* 2001;7:833-9.
6. Suzuki J, Bayna E, Dalle Molle E, Lew WYW. Nicotine inhibits cardiac apoptosis induced by lipopolysaccharide in rats. *J Am Coll Cardiol* 2003;41:482-8.
7. Chalon S, Moreno H, Benowitz NL, Hoffman BB, Blaschke TF. Nicotine impairs endothelium-dependent dilatation in human veins in vivo. *Clin Pharmacol Ther* 2000;67:391-7.
8. Benowitz NL, Fitzgerald GA, Wilson M, Zhang Q. Nicotine effects on eicosanoid formation and hemostatic function: comparison of transdermal nicotine and cigarette smoking. *J Am Coll Cardiol* 1993;22:1159-67.
9. Benowitz NL, Jacob P III, Yu L. Daily use of smokeless tobacco: systemic effects. *Ann Intern Med* 1989;111:112-6.
10. Wennmalm A, Benthin G, Granström EF, Persson L, Peterson A, Winell S. Relation between tobacco use and urinary excretion of thromboxane A<sub>2</sub> and prostacyclin metabolites in young men. *Circulation* 1991;83:1698-704.
11. Huhtasaari F, Lundberg V, Eliasson M, Janlert U, Asplund K. Smokeless tobacco as a possible risk factor for myocardial infarction. A population-based study in middle-aged men. *J Am Coll Cardiol* 1999;34:1784-90.
12. Huhtasaari F, Asplund K, Lundberg V, Stegmayr B, Wester PO. Tobacco and myocardial infarction: is snuff less dangerous than cigarettes? *BMJ* 1992;305:1252-6.
13. Joseph AM, Norman SM, Ferry LH, et al. The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. *N Engl J Med* 1996;335:1792-8.
14. Mahmarian JJ, Moye LA, Nasser GA, et al. Nicotine patch therapy in smoking cessation reduces the extent of exercise-induced myocardial ischemia. *J Am Coll Cardiol* 1997;30:125-30.
15. Mayhan WG, Patel KP. Effect of nicotine on endothelium-dependent arteriolar dilatation in vivo. *Am J Physiol* 1997;272:H2337-42.
16. Eliasson B, Taskinen MR, Smith U. Long-term use of nicotine gum is associated with hyperinsulinemia and insulin resistance. *Circulation* 1996;94:878-81.
17. Hellerstein MK, Benowitz NL, Neese RA, et al. Effects of cigarette smoking and its cessation on lipid metabolism and energy expenditure in heavy smokers. *J Clin Invest* 1994;93:265-72.
18. Suskin N, Sheth T, Negassa A, Yusuf S. Relationship of current and past smoking to mortality and morbidity in patients with left ventricular dysfunction. *J Am Coll Cardiol* 2001;37:1677-82.